REMARKS

Status of the Claims

Claims 1-20 and 58-90 are pending in the present application. Claims 21-57 have been cancelled without prejudice or disclaimer and will be pursued in a continuation application. Claim 18 has been amended as described elsewhere herein. New claims 68-90 have been added. Support for these new claims may be found in original claims 1-8 and 58-67, as well as lines 15-23 of page 21 of the specification. No new matter has been added by amendment.

The Rejection under 35 U.S.C. 112 Should be Withdrawn

Claims 18, 19, and 35 have been rejected under 35 U.S.C. §112, first paragraph, on the grounds that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Claim 35 has been cancelled without prejudice or disclaimer and will be prosecuted in a continuation application, thereby rendering the rejection of this claim moot. The rejection of claims 18 and 19 as amended is respectfully traversed. Furthermore, it is respectfully submitted that the rejection under 35 U.S.C. § 112, first paragraph, should not be applied to new claims 68-79 and 82-90 for the reasons described below.

The Examiner states that nucleotide sequences that hybridize to nucleotides 419-4835 of SEQ ID NO:1 under conditions of high stringency as recited in claim 18 are not sufficiently described because "[t]his genus embraces sub-sequences that are unknown and unsequenced polynucleotides, which may not encode a functional Factor VIII or which may generate an amino acid sequence that is irrelevant to the recited Factor VIII." December 12, 2001 Office Action, page 3.

In fact, claims 18, 19, 68-79, and 82-90 meet the requirements for adequate written description as provided in the Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, "Written Description Requirement," 66 Fed. Reg. 1099 (2001), and the supporting case law. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description' Requirement" state that a genus may be described by

"sufficient description of a representative number of species . . . or by disclosure of relevant, identifying characteristics , *i.e.* structure or other physical and/or chemical properties." 66 Fed. Reg. 1099, 1106 (2001). Moreover, the Guidelines state that "[d]isclosure of any combination of . . . identifying characteristics that distinguish the claimed invention from other materials and would lead one to the conclusion that the applicant was in possession" of the claimed invention is sufficient to satisfy the written description requirement. *Id.*

Applicants submit that the written description provided for the genus of sequences recited in claims 18, 19, 68-79, and 82-90 meets this requirement. Applicants have provided representative species of B-domain deleted factor VIII sequences falling within the claimed genus in SEQ ID NO:2 and on lines 24-30 of page 20 of the specification. Furthermore, the claims recite the identifying structural characteristics that define each genus of nucleotide sequences. These claims recite nucleotide sequences that hybridize to nucleotides 419-4835 of the nucleotide sequence set forth in SEQ ID NO:1 under conditions of high stringency and nucleotide sequences that are at least 75%, 80%, 85%, 90%, or 95% identical to nucleotides 419-4835 of the nucleotide sequence set forth in SEQ ID NO:1. These structural limitations are sufficient to distinguish the claimed nucleotide sequences from other materials and thus sufficiently define the claimed genus.

Moreover, in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), the court held that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." 119 F.3d at 1569. The recitation of the structural features of sequence identity with nucleotides 419-4835 of SEQ ID NO:1 or hybridization with nucleotides 419-4835 or SEQ ID NO:1 is sufficient to satisfy this requirement.

Applicants have further provided the functional characteristics that distinguish the claimed sequences of the genus. Specifically, claim 18 has been amended to specifically recite that the claimed nucleotide sequences encode biologically active B-domain deleted factor VIII,

and new claims 68-79, and 82-90 similarly recite that the claimed nucleotide sequences encode biologically active B-domain deleted factor VIII. Accordingly, claims 18, 19, 68-79, and 82-90 provide the relevant, identifying characteristics, both structural and functional, that describe the claimed genus, and one of skill in the art would recognize that the inventors were in possession of the claimed invention.

Claims 18, 19, and 35 have been rejected under 35 U.S.C. 112, first paragraph, on the grounds that the specification does not provide enablement for making and using nucleotide sequences that hybridize to nucleotides 419-4835 of SEQ ID NO:1 under conditions of high stringency. Claim 35 has been cancelled without prejudice or disclaimer and will be prosecuted in a continuation application, thereby rendering the rejection of this claim moot. The rejection of claims 18 and 19 as amended is respectfully traversed. Furthermore, it is respectfully submitted that the rejection under 35 U.S.C. § 112, first paragraph, should not be applied to new claims 68-79 and 82-90 for the reasons described below.

The Examiner argues that undue experimentation would be required to practice the invention because the Applicants fail to provide a reasonable guide for those seeking to practice the invention. In fact, sufficient guidance for making and using the recited sequence is given in the specification. Applicants have provided the sequence of a B-domain deleted human factor VIII in SEQ ID NO:2 and a nucleotide sequence encoding this polypeptide in nucleotides 419-4835 of SEQ ID NO:1. The variant nucleotide sequences recited in claims 18, 19, 68-79, and 82-90 vary from the nucleotide sequence set forth in SEQ ID NO:1 by structural parameters (i.e. the claimed nucleotide sequences hybridize to nucleotides 419-4835 of SEQ ID NO:1 under stringent conditions or share a specified level of identity with nucleotides 419-4835 of SEQ ID NO:1) that are defined in the specification, and the claims recite that the claimed nucleotide sequences encode polypeptides having the functional properties (i.e. the biologically-activity of B-domain deleted factor VIII) of the polypeptide having the amino acid sequence set forth in SEQ ID NO:2. Guidance for determining percent sequence identity and hybridization under stringent conditions is provided in the specification. *See*, pages 21-25. The specification also

describes conservatively-modified variants of the disclosed polypeptide and conservative substitutions of amino acids. *See*, lines 3-21 of page 23.

In addition to the B domain deleted factor VIII of SEQ ID NO:2, the specification discloses additional working examples of B-domain deleted factor VIII sequences including SEQ ID NO:4 and the sequences described on lines 24-30 of page 20 and lines 7-18 of page 22. A comparison of these B-domain deleted factor VIII polypeptides can be used to identify conserved regions that are likely to be required for B-domain deleted factor VIII function. The specification provides a description of factor VIII domains on lines 25-29 of page 2. The specification also provides methods for using mutagenesis to identify functional B-domain deleted factor VIII variants. *See*, lines 5-10 of page 23.

Finally, the specification provides assays for B-domain deleted factor VIII activity. *See*, lines 11-15 of page 20, Example 5 on pages 43-44, Example 10 on pages 46-47, Example 14 on page 49, and Example 15 on pages 49-50. Thus, a rational scheme for determining the regions of B-domain deleted factor VIII that would tolerate modification is provided. Based on the regions of SEQ ID NO:2 that are conserved with other B-domain deleted factor VIII polypeptides, working examples of B-domain deleted factor VIII sequences, and the guidance provided in the specification regarding factor VIII functional domains, the skilled artisan could choose among possible modifications to produce polypeptides within the structural parameters set forth in the claims and then test these modified variants to determine if they have the requisite biological activity of the polypeptide having the amino acid sequence given in SEQ ID NO:2. Although some quantity of experimentation would be required, the level of experimentation would not be undue in view of the amount of direction provided in the specification, the presence of working examples, the state of the prior art for B-domain deleted factor VIII sequences, and the level of skill of one of ordinary skill in the art. Further, the claims are directed only to those variants that retain the biological activity of B-domain deleted factor VIII. These factors all favor a conclusion that one of skill in the art could practice the claimed invention without undue experimentation and that the specification provides enablement commensurate with the scope of the claims.

In view of the above amendments and arguments, all grounds of rejection under 35 U.S.C. §112, first paragraph, have been overcome. Reconsideration and withdrawal of the rejections are therefore respectfully requested.

The Rejection Under 35 U.S.C. 102(e) Should be Withdrawn:

Claims 1, 3-18, 20-63, and 67 have been rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent Nos. 6,221,349 and 5,744,326. Claims 21-57 have been cancelled without prejudice or disclaimer and will be prosecuted in a continuation application, rendering the rejection of these claims moot. The rejection under 35 U.S.C. § 102(e) is respectfully traversed as applied to claims 1, 3-18, 20, 58-63, and 67. Furthermore, it is respectfully submitted that the rejection under 35 U.S.C. § 102(e) should not be applied to the new claims for the reasons described below.

First, Applicants submit that the disclosure of U.S. Patent No. 6,221,349 as it relates to AAV vectors comprising a coding sequence for B-domain deleted factor VIII (as well as methods of using these vectors) is not entitled to an effective date of October 20, 1998 because the priority application filed October 20, 1998 does not describe B-domain deleted factor VIII. Furthermore, even if the relevant subject matter disclosed in U.S. Patent No. 6,221,349 were entitled to the earliest claimed priority date of October 20, 1998, this patent does not anticipate the claims of the present invention because the Applicants had conceived of the invention and reduced it to practice prior to October 20, 1998. A declaration under 37 C.F.R. § 1.131, which demonstrates that Applicants had reduced the invention claimed in the present application to practice prior to October 20, 1998 accompanies the present response.

Claims 5, 17, 33, 48, and 49 have been rejected under 35 U.S.C. § 102(e) on the grounds that they are anticipated by U.S. Patent No. 5,744,326. Claims 33, 48, and 49 have been

cancelled without prejudice or disclaimer as described above, rendering the rejection of these claims moot, however, the rejection of claims 5 and 17 is respectfully traversed for the reasons described below.

Applicants submit that U.S. Patent No. 5,744,326 does not anticipate claims 5 and 17 under the applicable case law. The Federal Circuit has held that "[a]nticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." *Lindemann Maschinenenfabrik BmbH v.American Hoist & Derrick Co.*, 730 F.2d 1452 (Fed. Cir. 1984), citing *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542 (Fed. Cir. 1983). U.S. Patent No. 5,744,326 does not disclose either a recombinant adeno-associated virus vector comprising a heterologous nucleotide sequence encoding the B-domain deleted factor VIII polypeptide having the amino acid sequence set forth in SEQ ID NO:2, where the heterologous nucleotide sequence is operably linked with at least one enhancer and at least one promoter or a recombinant adeno-associated virus vector comprising a heterologous nucleotide sequence encoding the B-domain deleted factor VIII polypeptide having the amino acid sequence set forth in SEQ ID NO:2, where the heterologous nucleotide sequence is operably linked with a liver-preferred expression control element. Accordingly, the cited patent does not anticipate claims 5 and 17.

In view of the above arguments, all grounds for rejection under 35 U.S.C. 102(e) have been overcome. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Rejection Under 35 U.S.C. § 103 Should be Withdrawn

Claims 1-63, 65, and 67 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Number 6,221,349 in further view of U.S. Patent Number 6,258,595. Claims 21-57 have been cancelled without prejudice or disclaimer and will be prosecuted in a continuation application, rendering the rejection of these claims moot. The rejection under 35 U.S.C. § 103(a) is respectfully traversed as applied to claims 1, 3-18, 20, 58-63, and 67.

Furthermore, it is respectfully submitted that the rejection under 35 U.S.C. § 103(a) should not be applied to the new claims for the reasons described below.

As described above, the disclosure of U.S. Patent No. 6,221,349 as it relates to AAV vectors comprising a coding sequence for B-domain deleted factor VIII is not entitled to an effective date of October 20, 1998 because the priority application filed October 20, 1998 does not describe B-domain deleted factor VIII. Furthermore, even if the relevant subject matter disclosed in U.S. Patent No. 6,221,349 were entitled to the earliest claimed priority date of October 20, 1998, this patent does not anticipate the claims of the present invention because the Applicants had conceived of the invention and reduced it to practice prior to October 20, 1998 as evidenced by the declaration under 37 C.F.R. § 1.131 submitted herewith.

Accordingly, because the effective date of the relevant subject matter of U.S. Patent No. 6,221,349 is after the date of invention of the present application, the '349 patent is not available as prior art with respect to the claims of the present application. Therefore, it would not have been obvious to one of skill in the art to use the spacer taught by U.S. Patent No. 6,258,595 in the vector taught by the '349 patent.

In view of the above arguments, all grounds of rejection under 35 U.S.C. § 103 have been overcome. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Objections to the Claims Should be Withdrawn

Claim 43 was objected to for improperly depending on claim 43. This claim has cancelled and will be prosecuted in a continuation application, rendering the rejection moot.

Claims 64 and 66 are objected to as being dependent upon a rejected base claim; however, the rejections of claims from which claim 64 and 66 depend have been overcome, thereby obviating the objection.

CONCLUSION

It is believed that all the rejections have been obviated or overcome and the claims are in conditions for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Nora C. Martinez

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Version with Markings to Show Changes Made:

In the Claims:

Please amend claim 18 as follows:

18. A recombinant adeno-associated virus (rAAV) vector comprising a heterologous nucleotide sequence encoding a B-domain deleted factor VIII operably linked with an enhancer, wherein said nucleotide sequence is selected from the group consisting of:

(a) the nucleotide sequence given as nucleotides 419 to 4835 of the nucleotide sequence set forth in SEQ ID NO:1,

(b) a nucleotide sequence that hybridizes to the nucleotide sequence of (a) under conditions of high stringency and which encodes a biologically active B-domain deleted factor VIII[,]; and

(c) a nucleotide sequence that that differs from the nucleotide sequences of (a) and (b) above due to the degeneracy of the genetic code, and which encodes a biologically active B-domain deleted factor VIII.